

# Primary Synovial Sarcoma of the Thyroid Gland: Case Report and Review of the Literature

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## Key Words

Primary synovial sarcoma · Thyroid gland · Chemotherapy · Prognosis

## Abstract

Synovial sarcoma (SVS) of the thyroid gland is exceedingly rare. We report the case of a 55-year-old man with a rapidly growing 7-cm neck mass. Because of suspicion of anaplastic thyroid carcinoma, a total thyroidectomy was planned, without preoperative cytology. During surgery, the tumor ruptured, leading to fragmented and incomplete resection. The morphological and immunohistochemical aspects suggested thyroid SVS, which was confirmed by fluorescent in situ hybridization (SYT gene rearrangement). The patient experienced immediate local relapse in close contact with large vessels and the thyroid cartilage and was referred to our institution. Doxorubicin-ifosfamide chemotherapy led to a minor response that authorized secondary conservative surgery. Because of microscopically incomplete resection, adjuvant radiotherapy was chosen and is ongoing 10 months after initial surgery. The prognosis of thyroid SVS is associated with a high risk for local and metastatic relapses. Pretreatment diagnosis is fundamental and may benefit from molecular analysis. Margin-free monobloc surgical excision is the best chance for cure, but adjuvant chemotherapy and radiotherapy deserve to be discussed.

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## Introduction

Synovial sarcoma (SVS) represents ~10% of all soft-tissue sarcomas [1]. Most of them arise in the extremities, near the large joints. Unusual locations (15%) have been reported, notably including the head, neck, and trunk. Such locations make the recognition and differential diagnosis more difficult and the surgical treatment more complex because of the proximity of noble anatomic structures. Primary thyroid SVS is exceedingly rare. To our knowledge, only 4 cases have been reported in the English literature [2–5]. Here, we report an additional case of primary thyroid SVS – the first one treated with a combination of surgery and adjuvant chemo- and radiotherapy – and review the literature.

## Case Report

The patient was a 55-year-old Caucasian male with a personal medical history of high blood pressure and smoking. In December 2012, he underwent a cervicothyroid ultrasonography because of a rapidly growing palpable neck mass for 1 month, associated with dysphagia. Physical examination revealed a 7-cm, firm, macronodular, fixed, dipping thyroid mass. No cervical adenopathy was palpable. The WHO performance status was equal to 0. Ultrasonography revealed a 7-cm mass of the left thyroid lobe which was heterogeneous, hypervascularized, and mixed (solid and liquid). Biological thyroid tests, including serum tumor markers, were normal.

Because of suspicion of anaplastic thyroid carcinoma, a total thyroidectomy was planned in February 2013, without any preoperative cytology. Intraoperatively, the right thyroid lobe was hypertrophic, firm, but not nodular. The left lobe was under tension, ovalized, and enlarged (more than 12 cm) and extended from the top of the neck to the superior mediastinum. Its mobilization was difficult and led to capsular rupture and effusion of necrotic, hemorrhagic, and gelatinous liquid. Perioperative pathological analysis of tumor fragments showed a spindle cell proliferation suggesting sarcoma. Thyroidectomy was performed without lymph node dissection. Because of perioperative rupture and tumor fragmentation, the resection was classified as incomplete (R2). The postoperative course was uneventful.

Pathological examination (fig. 1) of multiple white-tan tumor fragments (between 2 and 3.5 cm each) revealed a dense cellular proliferation composed of ovoid-shaped to frankly spindle-shaped cells, without overt nuclear atypia, and disposed in a fascicular pattern. The mitotic index was moderate, inferior to 10 mitoses per 10 high-power fields. A rich vasculature was composed of branching vessels with a staghorn or hemangiopericytoma-like pattern. There were large hemorrhagic areas, without actual necrosis. On immunohistochemistry (IHC), tumor cells stained heterogeneously but strongly for epithelial membrane antigen (EMA). They were negative for pan-cytokeratin (AE1-AE3), CD34 (only staining the rich vasculature), desmin, H-caldesmon, PS100, HMB-45, and MDM2 antibodies. The diagnosis of monophasic SVS was suspected, and slides were sent to our expert institution for confirmation. Molecular analysis, performed on formalin-fixed paraffin-embedded tissue by fluorescent in situ hybridization (FISH), showed a *SYT* gene rearrangement, highly consistent with the diagnosis of a monophasic SVS, fibrous type. The histologic grade was 2 in the FNCLCC system (differentiation 3, mitosis count 1, and necrosis 0).

The patient was thus referred to our institution. Only 15 days after surgery, clinical examination detected a local disease evolution with palpation of a 4-cm neck mass, associated with dysphagia and pain. Whole-body computed tomography (CT) scan revealed

a 5-cm mass, in contact with the frontal parts of the left primitive carotid artery and internal jugular vein and the thyroid cartilage. No lymphadenopathy or distant metastasis was present. Cervical magnetic resonance imaging (MRI) confirmed a 4.2-cm mass in contact with large vessels and likely invasion of the paralaryngeal fat tissue above the thyroid cartilage (fig. 2a). Because of immediate postoperative relapse, local extension, and known relative chemosensitivity of SVS, we delivered primary chemotherapy combining doxorubicin and ifosfamide, before possible surgery. After 3 cycles, MRI and CT scan showed tumor size stabilization, with a small volume reduction ( $4 \times 3 \times 5.5$  vs.  $4.5 \times 3 \times 6$  cm), associated with extension of necrosis within the mass (60 vs. 20% before chemotherapy). MRI also showed a decrease in fat invasion and contact with the large vessels, whereas perichondrium invasion of the thyroid cartilage remained stable. Three additional chemotherapy cycles were thus delivered. After the last cycle, MRI and CT scan showed small tumor reduction ( $4 \times 2.5 \times 4.5$  vs.  $4 \times 3 \times 5.5$  cm) with further extension of tumor necrosis and improvement of tumor contact with the internal carotid artery and the internal jugular vein, without a resectability margin relative to the thyroid cartilage (fig. 2b). Chemotherapy was stopped and the patient was operated on. After discussion with the patient, it was decided to perform conservative surgery, without laryngectomy. Tumor resection was done including resection of the previous cutaneous scar, prelaryngeal muscles, thyroid cartilage perichondrium, superior horn of the thyroid cartilage, and left longer horn of the hyoid bone. An additional resection was performed in the thyroidectomy area with removal of fat and lymph nodes in the upper mediastinum. Ipsilateral cervical lymph node dissection was also performed. During the procedure, the left inferior laryngeal nerve was resected, but all other vascular and nervous elements could be preserved (fig. 3). No postoperative complications occurred and the patient was discharged after 5 days. Pathological examination of the operative specimen found a 7-cm monophasic SVS. Unfortunately, the resection margins (left cricothyroid muscle) were microscopically involved by tumor cells. No further mutilating surgery was chosen and treatment was completed with ongoing adjuvant radiotherapy.

## Discussion

Thyroid sarcomas, frequently reported before the 20th century, are in fact very rare. In 1940, Ewing reported that most of the published cases were mainly anaplastic carcinomas [2]. From that day, cases of originally thyroid sarcomas have been reported, including Kaposi sarcoma, leiomyosarcoma, and radiation-induced sarcoma, but they are very rare in incidence [6]. Thyroid SVS is extremely rare with to our knowledge only 5 cases, including the present case, reported in the English literature [2–5]. They are summarized in table 1. The median age of patients at the time of diagnosis is 55 years (range 15–72), which is older than the median age reported in other locations where SVS typically affects adolescents and young adults. No specific risk factor has been identified. All cases were clinically symptomatic, the major complaint for all patients being a firm mass rapidly growing in the anterior neck, suggestive of anaplastic thyroid carcinoma. Tumor growth seems faster in thyroid SVS than in the classic SVS location. No case with asthenia, anorexia, loss of weight, or thyroid dysfunction has been reported.

Radiological imaging is useful for the diagnosis and staging of thyroid tumors. Generally, the first exam is ultrasonography, which shows a heterogeneous nodule, with malignancy criteria such as important size or hypervascularization. CT and/or MRI allow the localization of the tumor in the thyroid gland and a better appreciation of the local extension before surgery. In our case, CT scan and MRI showed a voluminous local relapse and contact with

the large vessels and the thyroid cartilage. A whole-body scan can also find distant metastatic sites, as observed in 1 patient [2] with multiple bilateral lung nodular lesions only 2 weeks after diagnosis, in agreement with the high lung metastatic potential of sarcomas.

When SVS arises in an unusual site such as the thyroid, recognition and differential diagnosis are difficult, as demonstrated by the 5 cases reported, for which diagnosis was based on pathological, IHC, and molecular analyses of the operative specimen. Preoperative diagnosis based on fine-needle aspiration biopsy is very difficult: in the 2 cases where fine-needle aspiration biopsy was done, the suggested diagnosis was medullary carcinoma [3] and benign follicular lesion [4]. Histologically, our case showed only a spindle cell component without any identifiable epithelial structures, and thus was classified as a monophasic SVS, fibrous type. Previous cases located in the thyroid included 2 biphasic tumors with follicular-like structures, and 2 others with a monophasic spindle cell proliferation. Two cases displayed (at least focally) a hemangiopericytomatous vasculature as in our case, whereas 1 had calcifications. The suggestive IHC staining for EMA in the spindle cell population has been found in 3 cases [3, 4] including ours. Although morphological and IHC features could be highly unequivocal, the diagnosis of SVS needs to be confirmed by molecular analysis, detecting the *SYT-SSX* gene fusion (virtually found in all SVS) by real-time reverse transcriptase polymerase chain reaction (RT-PCR) or FISH, using frozen or paraffin-embedded tissues. All 5 reported cases show the specific fusion, except 1 in which molecular testing has not been performed [5]. Such analysis is feasible on tumor biopsy and should be performed in the case of diagnostic doubt since the preoperative diagnosis of sarcoma is fundamental.

Data on the prognosis of thyroid SVS are very limited with only 3 cases, including ours, informative regarding the follow-up after initial surgery. Two patients experienced both lung and local relapses at 0.5 months [2] and 18 months [3] and died 3 and 36 months, respectively, after surgery. Our patient experienced immediate local relapse after primary surgery, without any metastatic relapse after a 10-month follow-up. Overall, these data suggest that prognosis of thyroid SVS is very unfavorable, more unfavorable than other locations, potentially due to the uncommon form of presentation, rapid growth, delay in diagnosis, and difficulty in complete excision. Obviously, the small number of cases precludes any prognostic analysis.

Data on optimal treatment are also very limited. Like for any soft-tissue sarcoma, the main treatment is margin-free monobloc surgery, and the roles of adjuvant chemotherapy and radiotherapy are unclear. In all 5 cases reported, initial surgery was total thyroidectomy, associated with partial resection of neighbor organs in 2 cases [2, 3] and with cervical lymph node dissection in 2 cases [3, 4]. Unfortunately, the large tumor size and the proximity and invasion of neighbor noble organs and vessels made wide margin-free surgical resection very difficult, with perioperative tumor rupture in 2 cases. As usual for sarcomas, lymph node dissection is not recommended unless suspect lymph nodes are detected. Adjuvant radiotherapy and/or chemotherapy were not used in the 4 previously reported cases. Given the associated poor prognosis, the high risk for relapse for our patient, both local and metastatic, the relative chemosensitivity of SVS, and the evidence of benefit for adjuvant anthracycline-based chemotherapy in men older than 40 years after incomplete surgery of soft-tissue sarcoma [6], we delivered 6 cycles of doxorubicin-ifosfamide combination therapy before surgery. Chemotherapy led to disease stabilization with minor response that authorized secondary surgery. Because of microscopically incomplete resection and high risk for local relapse, adjuvant radiotherapy was performed.

In conclusion, we report the fifth case of primary SVS of the thyroid gland, and the third with a follow-up after diagnosis. As these tumors are exceptional and information about

diagnosis, prognosis, and standard treatment is lacking, we think that case reports such as this one may serve as the only reference for clinicians taking care of these patients. Preoperative diagnosis is fundamental to plan treatment and may benefit from molecular analysis. Radical surgical excision is the best chance for cure, but multimodality treatment deserves to be discussed given the high local and metastatic risks and overall poor prognosis. Like SVS of other sites, thyroid SVS seems responsive to doxorubicin-ifosfamide chemotherapy which should be used preoperatively in the cases where margin-free resection cannot be anticipated.

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### Disclosure Statement

The authors declare no conflict of interest.

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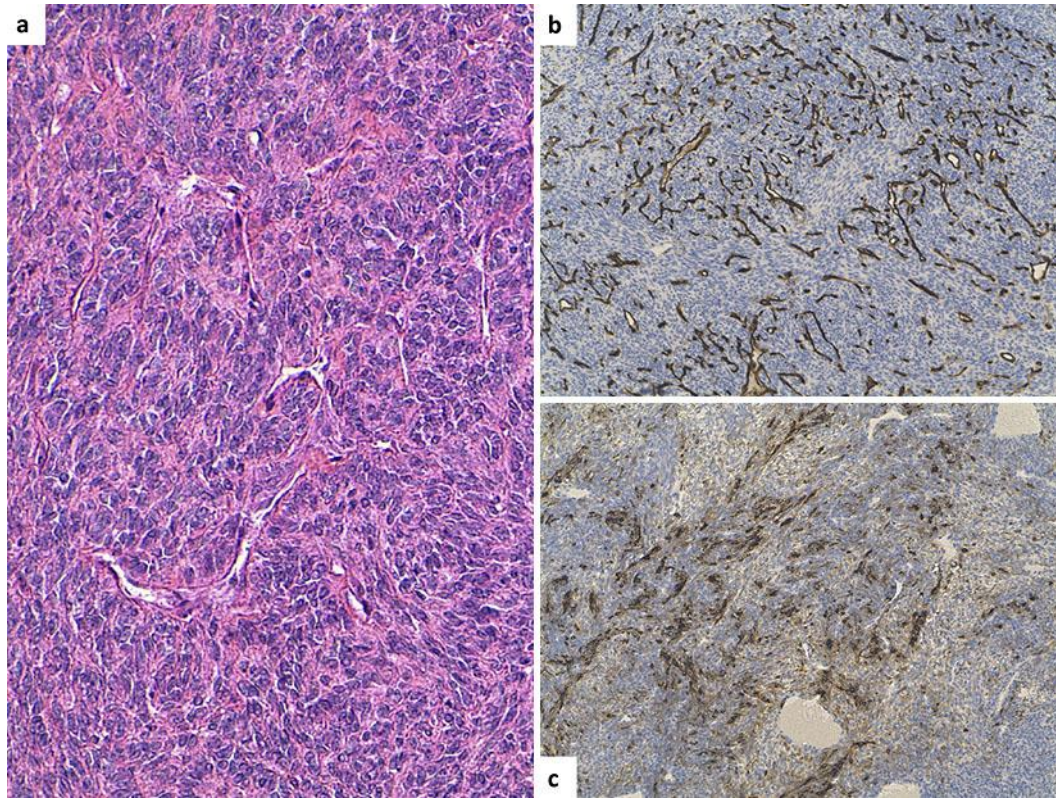
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**Table 1.** Five cases of thyroid SVS reported in the literature

Ref.	Sex/age, years	Initial clinical symptoms	Preoperative diagnosis by FNAB	Initial treatment	Pathological tumor size, cm/margins	Mono- or biphasic	Adjuvant treatment	Relapse (months after surgery)	Last follow-up (months after surgery)
[2]	F/72	neck mass, hoarseness, dysphagia	no FNAB	surgery	6/R2	mono-phasic	no	local and lung (0.5 months)	dead of unknown cause (3 months)
[3]	M/60	neck mass, hoarseness	no	surgery	6.8/R2	biphasic	no	local and lung (18 months)	dead of disease (36 months)
[4]	M/15	neck mass	no	surgery	6/R0	biphasic	n.a.	n.a.	n.a.
[5]	F/44	neck mass, dyspnea	no FNAB	surgery	17/R2	mono-phasic	n.a.	n.a.	n.a.
Our case	M/55	neck mass, dysphagia	no FNAB	surgery	7/R2	mono-phasic	no	local (0.5 months) CT, surgery, RT	alive without disease (10 months)

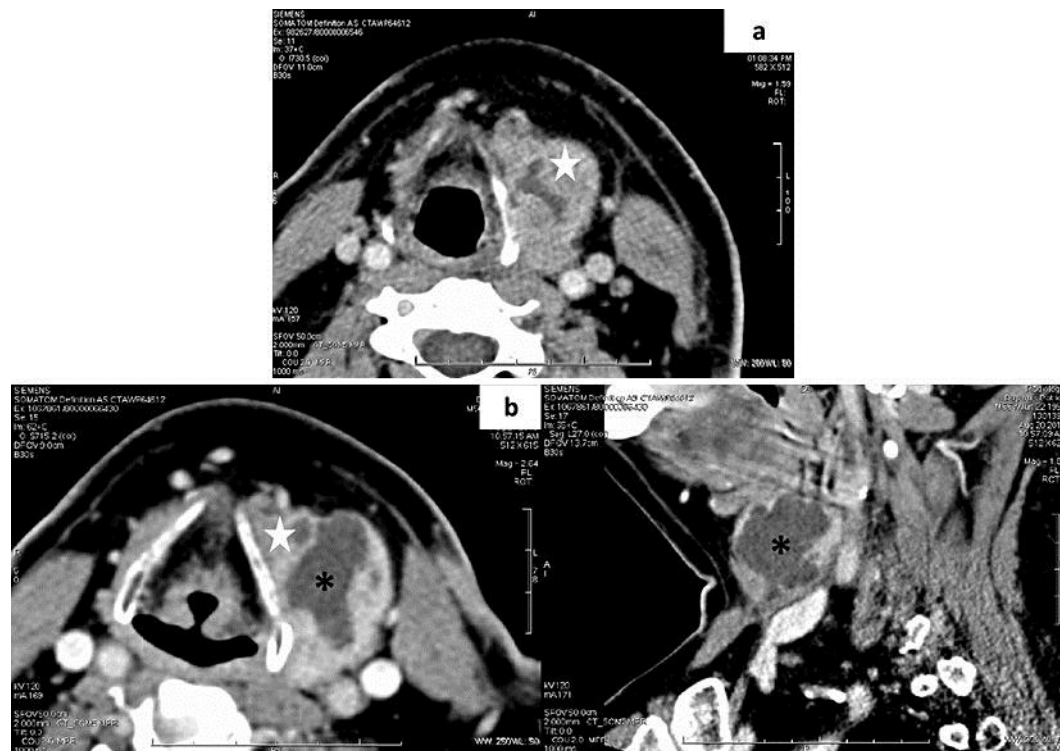
M = Male; F = female; FNAB = fine-needle aspiration biopsy; n.a. = not available; CT = chemotherapy; RT = radiotherapy.



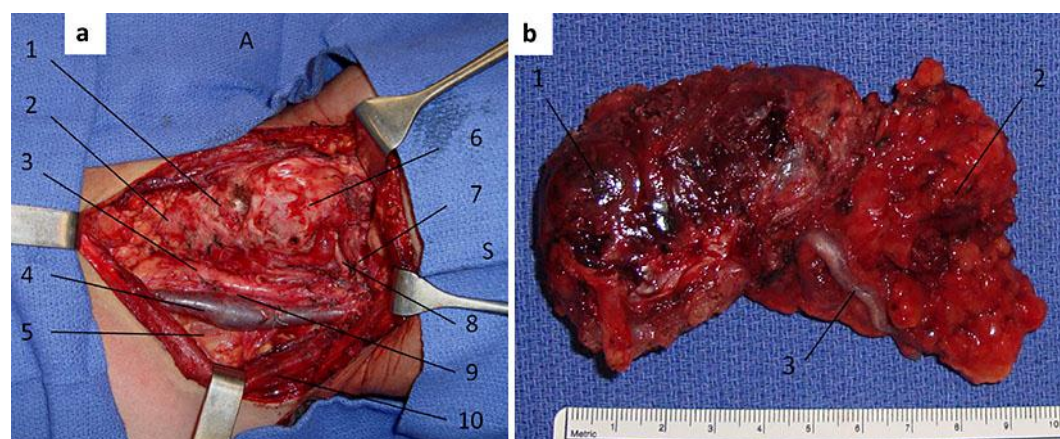


**Fig. 1.** Monophasic SVS of the thyroid: pathological aspects. **a** Highly cellular proliferation of ovoid undifferentiated cells admixed with arborized vessels (original magnification  $\times 200$ ). **b** CD34 IHC highlights the rich vascularization, but is negative on tumor cells (original magnification  $\times 100$ ). **c** EMA IHC shows weak and focal positivity on tumor cells (original magnification  $\times 100$ ).

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**Fig. 2.** Monophasic SVS of the thyroid: radiological aspects. **a** Before chemotherapy: enhanced cervical axial CT scan showing the mass (white star) with invasion of the thyroid cartilage and in contact with the frontal parts of the left primitive carotid artery and internal jugular vein. **b** After chemotherapy: enhanced axial cervical CT scan (left) showing an increase of the necrotic part (asterisk) in the tumor; sagittal cervical CT scan (right) showing persisting contact with the left jugular vein and no visible margin relative to the thyroid cartilage.



**Fig. 3.** Monophasic SVS of the thyroid: perioperative images. **a** Surgical photograph after tumor resection (left lateral view). A = Anterior; S = superior; 1 = cricoid cartilage; 2 = trachea; 3 = carotid artery; 4 = internal jugular vein; 5 = phrenic nerve; 6 = thyroid cartilage (after removal of the superior horn); 7 = hypoglossal nerve; 8 = superior laryngeal nerve; 9 = vagal nerve; 10 = sternocleidomastoid muscle. **b** Aspect of the tumor after removal. 1 = Tumor; 2 = thyroidectomy area with fat and lymph nodes of the upper mediastinum; 3 = cutaneous scar resection.